Myt1l safeguards neuronal identity by actively repressing many non-neuronal fates.

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Authors: Moritz Mall, Michael S Kareta, Soham Chanda, Henrik Ahlenius, Nicholas Perotti, Bo Zhou, Sarah D Grieder, Xuecai Ge, Sienna Drake, Cheen Euong Ang, Brandon M Walker, Thomas Vierbuchen, Daniel R Fuentes, Philip Brennecke, Kazuhiro R Nitta, Arttu Jolma, Lars M Steinmetz, Jussi Taipale, Thomas C Sudhof, Marius Wernig

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Public Summary:
Normal differentiation and induced reprogramming require the activation of target cell programs and silencing of donor cell programs. In reprogramming, the same factors are often used to reprogram many different donor cell types. As most developmental repressors, such as RE1-silencing transcription factor (REST) and Groucho (also known as TLE), are considered lineage-specific repressors, it remains unclear how identical combinations of transcription factors can silence so many different donor programs. Distinct lineage repressors would have to be induced in different donor cell types. Here, by studying the reprogramming of mouse fibroblasts to neurons, we found that the pan neuron-specific transcription factor Myt1-like (Myt1l) exerts its pro-neuronal function by direct repression of many different somatic lineage programs except the neuronal program. The repressive function of Myt1l is mediated via recruitment of a complex containing Sin3b by binding to a previously uncharacterized N-terminal domain. In agreement with its repressive function, the genomic binding sites of Myt1l are similar in neurons and fibroblasts and are preferentially in an open chromatin configuration. The Notch signalling pathway is repressed by Myt1l through silencing of several members, including Hes1. Acute knockdown of Myt1l in the developing mouse brain mimicked a Notch gain-of-function phenotype, suggesting that Myt1l allows newborn neurons to escape Notch activation during normal development. Depletion of Myt1l in primary postmitotic neurons de-repressed non-neuronal programs and impaired neuronal gene expression and function, indicating that many somatic lineage programs are actively and persistently repressed by Myt1l to maintain neuronal identity. It is now tempting to speculate that similar 'many-but-one' lineage repressors exist for other cell fates; such repressors, in combination with lineage-specific activators, would be prime candidates for use in reprogramming additional cell types.

Scientific Abstract:
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